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New research addresses the wrenching question left when someone ends his or her own life

WHY???

The neuroscience of suicide

By Carol Ezzell

MATT MAHURIN

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In 1994, two days after returning from a happy family vacation, my 57-year-old mother put the muzzle of a handgun to her left breast and fired, drilling a neat and lethal hole through her heart—and, metaphorically, through our family's as well.

SUICIDE IS THE **11TH LEADING CAUSE OF DEATH** IN THE U.S., ACCOUNTING FOR 1.2 PERCENT OF ALL FATALITIES.

A PERSON DIES BY SUICIDE ROUGHLY **EVERY 18 MINUTES** IN THE U.S. SOMEONE ATTEMPTS SUICIDE EVERY MINUTE.

FOUR MALES DIE BY SUICIDE FOR EVERY FEMALE, BUT AT LEAST **TWICE AS MANY WOMEN** AS MEN ATTEMPT SUICIDE.

APPROXIMATELY **80 AMERICANS** TAKE THEIR OWN LIVES **EVERY DAY**.

THE SUICIDE RATE FOR **WHITE MALES AGED 15 TO 24** HAS TRIPLED SINCE 1950.

It was around midnight on a Saturday night in July, the time of year, I was later surprised to learn, that has the highest incidence of suicide in the Northern Hemisphere. My stepfather was at home but didn't hear the single shot because he was taking a shower in a bathroom at the other end of the house. When he returned to their bedroom, she was crumpled on the carpet in her pajamas, almost gone. She tried to say something to him before she died, but he couldn't make out what it was. The emergency medical technicians arrived to find a patient, but not the one they expected: my stepfather nearly died himself that night after hyperventilating from the shock, which all but overwhelmed lungs already compromised by emphysema.

Through it all, I was asleep in my apartment 200 miles away. I was awakened at 2 A.M. by a call from my building's front desk, telling me that my sister-in-law was downstairs and wanted to come up. My first words to her when I opened my door were, "It's Mother, isn't it?"

Our family has too much company in suffering the agony of having a loved one die by suicide: annually, 30,000 people in the U.S. take their own lives. That is roughly half again the number who died of AIDS last year. Why do they do it?

Like an estimated 60 to 90 percent of U.S. suicides, my mother had a mental illness. In her case, it was manic-depression, also called bipolar disorder. Unless they are taking—and responding well to—the appropriate medication, manic-depressives oscillate between troughs of despair and peaks of elation or agitation. Most who end their lives have a history of depression or manic-depression, but people with severe depression differ in their propensity for suicide.

Scientists have begun uncovering behavioral tip-offs and are also exploring clues to anatomical and chemical differences between the brains of suicides and of those who die of other causes. If such changes could be detected in medical imaging scans or through blood tests, doctors might one day be able to identify those at highest risk of dying by suicide—and therefore attempt to prevent the tragedy from occurring. Sadly, that goal is not immediately in sight: many who have suicidal tendencies still end up taking their own lives, despite intensive intervention.

My Mother's Legacy

THE QUESTION of what drove my mother to her desperate act that humid night nearly nine years ago is the second most difficult thing I live with. Scarcely a day has gone by that I haven't been pierced by the anguish of wanting to know exactly what prompted her suicide on that particular night as well as the crushing guilt over what I could have done—should have done, would have done—to stop her. The hardest thing I have to live with is the realization that I will never know the answer for sure.

In the future, some parts of her story should become less mysterious, because researchers are studying those very issues. One age-old question, whether a tendency to commit suicide is inborn or the result of an accumulation of bad experiences, is at least closer to resolution.

Although the nature-versus-nurture debate still rages in some psychiatric circles, most researchers who study suicide fall somewhere in the middle. "You need several things to go wrong at once," explains Victoria Arango of the New York State Psychiatric Institute, which is affiliated with Columbia-Presbyterian Medical Center. "I'm not saying that suicide is purely biological, but it starts with having

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PHYSICAL CLUES TO SUICIDE

IN PEOPLE WHO DIE BY SUICIDE, anatomical and chemical changes occur in two brain regions: the orbital prefrontal cortex, which lies just above the eyes, and the dorsal raphe nucleus of the brain stem. The alterations are evidence of a reduced ability to make and use serotonin, a key neurotransmitter known to be lacking in the brains of impulsive people and in those suffering from depression. Neurons in the dorsal raphe nucleus produce serotonin; they have long projections (*blue arrow*) that carry the neurotransmitter to the orbital prefrontal cortex. In suicide victims, the dorsal raphe nucleus sends less than normal amounts of serotonin to the orbital prefrontal cortex. *—C.E.*

CHANGES IN THE ORBITAL PREFRONTAL CORTEX

Slices from the brain of a suicide victim contain fewer neurons in a subsection (*circled*) of the orbital prefrontal cortex.

Throughout the cortex, serotonin transporters (*gold*) absorb serotonin. In the marked subsection, the number of these transporters is reduced.

The analyzed area also exhibits more binding of serotonin (*orange*) per neuron. Together the analyses indicate that the brain tried to make the most of the serotonin it had.

SINGLE HEMISPHERE OF BRAIN

CHANGES IN THE DORSAL RAPHE NUCLEUS

Neurons in the dorsal raphe nucleus of the brain stem of someone who died by suicide contain more of the enzyme that synthesizes serotonin (*dark staining*) than the corresponding brain region of someone who died of another cause. The difference indicates that the brains of suicides are attempting to produce more serotonin.

VICTORIA ARANGO ET AL. *New York State Psychiatric Institute* (*brain slices*); REPRODUCED WITH PERMISSION FROM *BIOLOGICAL PSYCHIATRY*, VOL. 46, NO. 4; 1999 (*neuron micrographs*); CLEO VILETT (*brain diagram*)

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BETWEEN 1980 AND 1996 THE SUICIDE RATE FOR **AFRICAN-AMERICAN MALES** AGED 15 TO 19 INCREASED 105 PERCENT.

SUICIDE IS THE **THIRD-RANKING CAUSE OF DEATH FOR TEENS** AGED 10 TO 19.

WHITE MEN 85 AND OLDER DIE BY SUICIDE AT SIX TIMES THE OVERALL NATIONAL RATE.

SUICIDE RATES FOR WOMEN PEAK BETWEEN THE AGES OF 45 AND 54 AND SURGE AGAIN AFTER AGE 85.

ALCOHOLISM IS A FACTOR IN ROUGHLY 30 PERCENT OF ALL COMPLETED SUICIDES.

APPROXIMATELY 7 PERCENT OF **PEOPLE WITH ALCOHOL DEPENDENCE** WILL DIE BY SUICIDE.

EIGHTY-THREE PERCENT OF **GUN-RELATED DEATHS** IN THE HOME ARE THE RESULT OF SUICIDE.

DEATH BY FIREARMS IS THE **FASTEST-GROWING METHOD** OF SUICIDE.

an underlying biological risk." Life experience, acute stress and psychological factors each play a part, she asserts. At the root of the mystery of suicide, however, lies a nervous system whose lines of communication have become tangled into unbearably painful knots.

Arango and her Columbia colleague J. John Mann are leading the effort to pick apart those knots and discern the neuropathology of suicide. They have assembled what is generally acknowledged to be the country's best collection of brain specimens from suicide victims. Twenty-five deep freezers in their laboratories hold a total of 200 such brains, which the researchers are examining for neuroanatomical, chemical or genetic alterations that might be unique to those compelled to end their lives. Each brain is accompanied by a "psychological autopsy," a compendium of interviews with family members and intimates probing the deceased's state of mind and behavior leading up to his or her final act. "We try to get a complete picture," Mann says, "and come up with an aggregate explanation for that person." A suicide brain is matched against a control brain from a person of the same sex without a psychiatric disorder who died at approximately the same age of a cause other than suicide.

Contained within the three-pound gelatinous mass of the human brain are the cells and molecules that were inextricably linked to what that person once thought—and, indeed, once was. Mann's and Arango's research concentrates in part on the prefrontal cortex, the portion of the brain encased in the bone of the forehead. The prefrontal cortex is the seat of the so-called executive functions of the brain, including the internal censor that keeps individuals from blurting out what they really think in awkward social situations or acting on potentially dangerous impulses.

The impulse-dampening role played by the prefrontal cortex particularly interests Mann and Arango. Scientists have looked to impulsivity as a predictor for suicide for decades. Although some people plan their deaths carefully—leaving notes, wills and even funeral plans—for many, including my mother, suicide appears to be spontaneous: a very bad decision on a very bad day. So Arango and Mann search in these brains for clues to the biological basis for that impulsivity. One focus is on differences in the availability of the brain chemical serotonin—previous research on the basis of impulsivity has indicated a dearth of it.

Serotonin is a neurotransmitter, one of the molecules that jumps the tiny gaps known as synapses between neurons to relay a signal from one such brain cell to another. Tiny membranous bubbles called vesicles erupt from each signal-sending, or presynaptic, neuron, releasing serotonin into the synapse. Receptors on the receiving, or postsynaptic, neurons bind to the neurotransmitter and register biochemical changes in the cell that can change its ability to respond to other stimuli or to turn genes on or off. After a short while, the presynaptic cells reabsorb the serotonin using molecular sponges termed serotonin transporters.

Serotonin somehow exerts a calming influence on the mind. Prozac and similar antidepressant drugs work by binding to serotonin transporters and preventing presynaptic neurons from soaking up the secreted serotonin too quickly, allowing it to linger a bit longer in the synapse and continue to transmit its soothing effect.

Traces of Pain

MORE THAN two decades of reports have linked low serotonin levels in the brain to depression, aggressive behavior and a tendency toward impulsiveness, but the evidence has been particularly confusing with regard to suicide. A number of studies have found reductions in serotonin in the brains of suicides, whereas others have not. Some have observed a lack of serotonin in one part of the brain but not elsewhere. Still others have described increases in the number of receptors for serotonin or deficits in the chain of chemical events that convey the serotonin signal from those receptors to the inside of a neuron.

Despite the inconsistencies, the bulk of evidence points strongly to a problem in the brains of suicides involving the serotonin system. That line of thinking has been bolstered by the recent findings of Arango and Mann.

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THE "MAGIC" OF LITHIUM

Lithium appears to prevent suicide. Why do so few suicidal people take it?

"Lithium ... is the lightest of the solid elements, and it is perhaps not surprising that it should in consequence possess certain modest magical qualities." —G. P. Hartigan, psychiatrist

"Only crazy people take lithium!" my mother shouted during one of our many arguments over her not receiving the best treatment for her manic-depression. She accused me and my stepfather of wanting to medicate her so she would "just shut up." To be honest, she was partially right: it is very trying to be around someone in the grip of a mania, which often brings on incessant, stream-of-consciousness talking.

Many people find lithium—which generally comes in capsules of lithium carbonate or lithium citrate—difficult to take. It can cause hand tremors, constant thirst, frequent urination, weight gain, lethargy, reduced muscle coordination, blurred thinking and short-term memory deficits. People on it must also have its concentration in their blood assessed regularly to ensure that it is within the therapeutic range: the drug is usually ineffective below 0.6 millimole per liter of blood serum and can cause life-threatening toxic reactions if the level becomes higher than two millimoles per liter.

Lithium is used routinely to even out the extreme mood swings of patients with manic-depressive illness, or bipolar disorder. Increasingly, however, it is also offered to people with depression. But a growing body of evidence indicates that this compound can literally keep people who are at risk of suicide alive. In 1998 lithium pioneer Mogens Schou of the Psychiatric Hospital in Risskov, Denmark, pulled together the results of various studies of lithium as a suicide preventive and observed that people not taking the drug were three to 17 times as likely to end their own lives as depressed people who took the medication. Likewise, Schou determined that lithium reduced suicide attempts by a factor of between six and 15.

How does it exert its salutary effects? Despite a number of tantalizing leads, researchers are still not certain. "It's hard to say at this time," says Ghanshyam N. Pandey of the University of Illinois. "There are so many modes of action." Lithium is thought to affect tiny ports called ion channels on the surfaces of nerve cells, or neurons. As they open and close, ion channels admit or bar charged atoms that determine the electrical potential within the cells, thereby dictating their activity and ability to communicate with other neurons. Scientists posit that the drug stabilizes the excitability of the neurons by influencing the ion channels or by skewing the chain reaction of biochemical events that occur within an excited cell.

A drug only works, though, if someone takes it properly. In the May 2002 issue of the *Journal of Clinical Psychiatry,* Jan Scott and Marie Pope of the University of Glasgow reported that half of a group of 98 patients who were taking a mood-stabilizing drug such as lithium failed to stick with their drug regimen. Yet, the researchers noted, just 1 percent of scientific publications on the subject of mood stabilizers looked at why patients did not take their lithium as prescribed.

LITHIUM is the lightest of the solid elements and, in its pure form, floats (*left*). When compounded in pill form as lithium carbonate or lithium citrate (*above*), it can be taken to stabilize moods.

J. John Mann of the New York State Psychiatric Institute says that a major factor in noncompliance is the human desire not to want to think of oneself as ill. "There's a natural reluctance to take any medicine long-term," Mann explains. "When a person is depressed, they have a problem imagining ever getting better. When they're well, they can't imagine getting sick again."

The side effects of lithium also play a role. Kay Redfield Jamison, a psychiatrist at Johns Hopkins University who studies manic-depression and suicide—and who is a manic-depressive herself—has found that the most common reasons patients stop taking the drug are cognitive side effects, weight gain and impaired coordination. In her moving memoir, *An Unquiet Mind,* she recounts her own struggle to come to terms with the fact that she will probably be coping with lithium's side effects for the rest of her life. Perhaps if my mother had lived to read it, she would have been heartened by Jamison's example and motivated to begin lithium therapy. *—C.E.*

THOMAS SIELNACHT (*container*); CUSTOM MEDICAL STOCK PHOTO (*pill*)

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SUICIDES **OUTNUMBER HOMICIDES TWO TO ONE** EVERY YEAR IN THE U.S.

SUICIDE ACCOUNTS FOR **NEARLY 57 PERCENT OF ALL FIREARM DEATHS** IN THE U.S.; 60 PERCENT OF ALL SUICIDES INVOLVE FIREARMS.

In a second-floor laboratory at the upper tip of Manhattan, Arango's technician leans into an open freezer to use a machine called a microtome to pare a feather-light slice from a frozen brain donated by grieving relatives anxious to help science address the mystery of suicide. Using a chilled brush, she delicately coaxes the rime of icy tissue onto a glass slide the size of a snapshot. With the body heat from her own gloved hands, she then melts the brain sliver onto the glass; observing the process is reminiscent of watching bright sunlight on a frigid winter day dissolve frost on a window.

The scientists working with the Columbia collection divide the brains into left and right hemispheres and then carefully section each hemisphere into 10 or 12 blocks from front to back. Once frozen and put through the microtome, every block yields roughly 160 slices that are thinner than a human hair.

The chief benefit of this approach is that Arango's and Mann's groups can perform several different biochemical tests on the same brain slice and know the exact anatomical locations of the variations they find. By reassembling the slices virtually, they can compile an overall model of how those abnormalities might work in concert to affect a complex behavior.

At a conference of the American College of Neuropsychopharmacology in 2001, Arango reported that the brains of people who were depressed and died by suicide contained fewer neurons in the orbital prefrontal cortex, a patch of brain just above each eye. What is more, in suicide brains, that area had one third the number of presynaptic serotonin transporters that control brains had but roughly 30 percent more postsynaptic serotonin receptors.

Together the results suggest that the brains of suicides are trying to make the most of every molecule of serotonin they have, by increasing the molecular equipment for sensing the neurotransmitter while decreasing the number of transporters that absorb it back again. "We believe there is a deficiency in the serotonergic system in people who commit suicide," Arango concludes. "They can be so sick Prozac can't help them." Inhibiting the reuptake of serotonin isn't always enough to prevent suicide: it wasn't for my mother, who died despite taking 40 milligrams of Prozac a day.

Mann and his colleagues are now trying to devise a positron emission tomography (PET) test that might one day aid doctors in determining which among their depressed patients have the most skewed serotonin circuitry—and are therefore at highest risk of suicide. PET scans mirror brain activity by monitoring which brain regions consume the most blood glucose; administering drugs, such as fenfluramine, that cause the release of serotonin can help scientists zero in on active brain areas using serotonin.

In the January *Archives of General Psychiatry,* Mann and his co-workers reported a relation between activity in the prefrontal cortex of people who had attempted suicide and the potential deadliness of the attempt. Those who had used the most dangerous means—for example, by taking the most pills or jumping from the highest point—had the least serotonin-based activity in the prefrontal cortex. "The more lethal the suicide attempt, the bigger the abnormality," Mann observes.

Ghanshyam N. Pandey of the University of Illinois agrees that the brain's serotonin system is key to understanding suicide. "There is a lot of evidence to suggest serotonin defects in suicide, but these defects do not exist in isolation but in concert with other deficits," he says. "The whole system appears to be altered."

The serotonin hypothesis does not rule out important contributions by other neurotransmitters, however. Serotonin is only one molecule in the intricate biochemical network named the hypothalamic-pituitary-adrenal (HPA) axis, in which the hypothalamus and pituitary glands in the brain communicate with the adrenal glands atop the kidneys. The HPA is responsible for the so-called fight-or-flight response exemplified by the racing heartbeat and sweaty palms you get after a close scrape while driving, say. In particular, corticotrophin-releasing factor, which the hypothalamus releases in times of stress, causes the anterior pituitary to make adrenocorticotropic hormone, which in turn causes the adrenal cortex to produce glucocorticoids such as cortisol. Cortisol prepares the body for stress by raising blood sugar concentrations, increasing heart rate and inhibiting the overreaction of the immune response.

Serotonin fits into the HPA because it modulates the threshold of stimulation. Researchers such as Charles B. Nemeroff of the Emory University School of Medicine and his colleagues are finding that extremely adverse early life experiences, such as child abuse, can throw the HPA axis off kilter, literally leaving biochemical imprints on the brain that make it vulnerable to depression as a result of overreacting to stress later on.

In 1995 Pandey's group reported indications that the abnormalities in serotonin circuitry present in those at risk for suicide could be detectable using a relatively simple blood test. When he and his co-workers compared the number of serotonin receptors on platelets (clotting cells) in the blood of suicidal people with those of nonsuicidal people, they observed that individuals considering suicide had many more serotonin receptors. (Platelets just happen to have receptors for serotonin, although it is unclear why.)

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Pandey says that his group concluded that the boost in receptors reflects a similar increase in the suicide-prone brains—a vain attempt to garner as much serotonin as possible. To prove the link, Pandey would like to determine whether the association holds up in people who go on to take their own lives. "We want to know if platelets can be used as markers for identifying suicidal patients," Pandey says. "We are making progress, but it's slow."

A Curse of Generations

UNTIL RESEARCHERS can develop tests to forecast those at highest risk for suicide, doctors might concentrate their efforts on the biological relatives of suicide victims. In the September 2002 issue of *Archives of General Psychiatry*, Mann, David A. Brent of the Western Psychiatric Institute and Clinic in Pittsburgh and their colleagues reported that the offspring of suicide attempters have six times the risk of people whose parents never attempted suicide. The link appears in part to be genetic, but efforts to pin down a predisposing gene or genes have not yet yielded any easy answers. In studies in the early 1990s Alec Roy of the Department of Veterans Affairs Medical Center in East Orange, N.J., observed that 13 percent of the identical twins of people who died by suicide also eventually took their own lives, whereas only 0.7 percent of fraternal twins traveled the same path as their suicidal siblings.

These statistics serve as warnings to me and to others with biological ties to suicide. In a small jar in my bedroom I keep a bullet from the same box that contained the one that killed my mother. The police took the gun after her death, and I myself threw away the remaining bullets while cleaning out her bedroom closet. But I like to think that I hold on to that single, cold pellet of metal as a reminder of how tenuous life is and how one impulsive act can have immense and rippling consequences. Perhaps someday science will better understand the basis for such harrowing acts so that families like mine will be spared. SA

Carol Ezzell is a staff editor and writer.

MATT MAHURIN

MORE TO EXPLORE

Night Falls Fast: Understanding Suicide. Kay Redfield Jamison. Vintage Books, 2000.

Reducing Suicide: A National Imperative. Institute of Medicine. Edited by Sarah K. Goldsmith, Terry C. Pellmar, Arthur M. Kleinman and William E. Bunney. National Academies Press, 2002.

Information and education materials on preventing suicide can be obtained from the National Mental Health Association (**www.nmha.org**), the American Foundation for Suicide Prevention (**www.afsp.org**) and the American Association of Suicidology (**www.suicidology.org**). The groups also have support materials for the survivors of loved ones who died by suicide.

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